DOCKET NO.: ISIS0003-103 (ISPH-0522US.D2) **PATENT**

In the Claims:

The current status of all claims is listed below and supercedes all previous lists of claims.

Please add new claim 76 as follows:

1. (original) A method of modulating RNA interference in a cell or tissue comprising contacting said cell or tissue with an amount of a modulator effective to modulate RNA interference by at least 50% as compared to a control wherein the modulator is a human RNase III polypeptide or an oligomeric compound targeted to a nucleic acid encoding human RNase III.

2. (original) The method of claim 1 wherein modulation of RNA interference is determined by detecting a difference of at least 50% between a level of a RNA fragment in the presence of the modulator and the level of the RNA fragment in the absence of the modulator, a difference being indicative of modulation of RNA interference.

3. (original) The method of claim 1 wherein modulation of RNA interference is determined by detecting a difference of at least 50% between a level of a target RNA in the presence of the modulator and the level of the target RNA in the absence of the modulator, a difference being indicative of modulation of RNA interference.

4. (original) The method of claim 1 wherein the cell or tissue is a human cell or tissue.

5. (original) The method of claim 1 wherein the RNase III polypeptide cleaves double-stranded RNA.

6. (original) The method of claim 1 wherein the RNase III polypeptide comprises an amino acid sequence which is at least 90% homologous to SEQ ID NO: 2.

7. (original) The method of claim 1 wherein the RNase III polypeptide comprises SEQ ID NO: 2.

8. (original) The method of claim 1 wherein the RNase III polypeptide comprises amino acid residues 949-1374 of SEQ ID NO:2, amino acid residues 1-220 of SEQ ID NO:2 or amino acid residues 221-470 of SEQ ID NO:2.

9. (original) The method of claim 1 wherein the RNase III polypeptide is exogenously added.

10. (original) The method of claim 9 wherein the RNase III polypeptide is expressed by an exogenously added vector encoding said polypeptide.

11. (original) The method of claim 1 wherein the oligomeric compound is 8 to 50 nucleobases in length and targeted to a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the compound inhibits the expression of human RNase III by at least 50%.

12. (original) The method of claim 11 wherein the oligomeric compound comprises SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 or SEQ ID NO:17.

13. (original) The method of claim 11 wherein the oligomeric compound comprises at least one modified internucleoside linkage.

14. (original) The method of claim 13 wherein the modified internucleoside linkage is a phosphorothioate linkage.

15. (original) The method of claim 11 wherein the oligomeric compound comprises at least one modified sugar moiety.

16. (original) The method of claim 15 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

17. (original) The method of claim 11 wherein the oligomeric compound is targeted to a 3'-untranslated region (3'UTR), a 5'-untranslated region (5'UTR) or a coding region of a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the oligomeric compound inhibits the expression of human RNase III by at least 50%.

18. (original) A method of modulating processing of an RNA in a cell or tissue comprising contacting said cell or tissue with an amount of a modulator effective to modulate RNA processing by at least 50% as compared to a control, wherein the modulator is a human RNase III polypeptide or an oligomeric compound targeted to a nucleic acid encoding human RNase III.

19. (original) The method of claim 18 wherein modulation of processing is determined by detecting a difference of at least 50% between a level of a target RNA in the presence of the modulator and the level of the target RNA in the absence of the modulator, a difference indicative of modulation of RNA processing.

20. (original) The method of claim 18 wherein modulation of RNA processing is determined by detecting a difference of at least 50% between a level of a fragment of the RNA in the presence of the modulator and the level of the fragment in the absence of the modulator, a difference indicative of modulation of RNA processing.

21. (original) The method of claim 18 wherein the RNase III polypeptide cleaves double-stranded RNA.

22. (original) The method of claim 18 wherein the RNase III polypeptide comprises an amino acid sequence which is at least 90% homologous to SEQ ID NO: 2.

23. (original) The method of claim 18 wherein the RNase III polypeptide comprises SEQ ID NO: 2.

24. (original) The method of claim 18 wherein the RNase III polypeptide comprises amino acid residues 949-1374 of SEQ ID NO:2, amino acid residues 1-220 of SEQ ID NO:2 or amino acid residues 221-470 of SEQ ID NO:2.

25. (original) The method of claim 18 wherein the oligomeric compound is 8 to 50 nucleobases in length and is targeted to a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the compound inhibits the expression of human RNase III by at least 50%.

26. (original) The method of claim 25 wherein the oligomeric compound comprises SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 or SEQ ID NO:17.

27. (original) The method of claim 25 wherein the oligomeric compound comprises at least one chemical modification.

28. (original) The method of claim 25 wherein the oligomeric compound is targeted to a 3'-untranslated region (3'UTR), a 5'-untranslated region (5'UTR) or a coding region of a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the oligomeric compound inhibits the expression of human RNase III by at least 50%.

29. (original) The method of claim 18 wherein the RNA is rRNA, snRNA, snoRNA, or miRNA, or precursors of rRNA, snRNA, snoRNA, or miRNA

30. (original) The method of claim 18 wherein 32S RNA is processed to form one or more 30S and 32S RNA fragments.

31. (original) The method of claim 30 wherein 32S RNA is processed to form one or more 12S pre-rRNA and 28S rRNA fragments.

32. (original) The method of claim 18 wherein the RNA is processed into one or more fragments of about 50-100 nucleotides in length.

33. (original) The method of claim 18 wherein the RNA is processed into one or more fragments of about 70 nucleotides in length.

34. (original) The method of claim 18 wherein said processing yields one or more fragments of said RNA.

35. (original) The method of claim 34 wherein one or more nucleotide fragments from 21 nucleotides to 23 nucleotides in length are generated from the RNA.

36. (original) The method of claim 34 wherein the RNA processing is in a cell nucleus.

37. (original) The method of claim 34 wherein the RNA processing is in a nucleolus.

38. (original) A method of modulating RNA expression in a cell or tissue comprising contacting said cell or tissue with an amount of a modulator effective to modulate RNA expression by at least 50% as compared to a control, wherein the modulator is a human RNase III polypeptide or an oligomeric compound targeted to a nucleic acid encoding human RNase III.

39. (original) The method of claim 38 wherein modulation of RNA expression is determined by detecting a difference of at least 50% between a level of a fragment of the RNA in the presence of the modulator and the level of the fragment in the absence of the modulator, a difference being indicative of modulation of RNA expression.

40. (original) The method of claim 38 wherein modulation of RNA expression is determined by detecting a difference of at least 50% between a level of a target RNA in the

presence of the modulator and the level of the target RNA in the absence of the modulator, a difference being indicative of modulation of RNA expression.

41. (original) The method of claim 38 wherein the cell or tissue is a human cell or tissue.

42. (original) The method of claim 38 wherein the RNase III polypeptide cleaves double-stranded RNA.

43. (original) The method of claim 38 wherein the RNase III polypeptide comprises an amino acid sequence which is at least 90% homologous to SEQ ID NO: 2.

44. (original) The method of claim 38 wherein the RNase III polypeptide comprises SEQ ID NO: 2.

45. (original) The method of claim 38 wherein the RNase III polypeptide comprises amino acid residues 949-1374 of SEQ ID NO:2, amino acid residues 1-220 of SEQ ID NO:2 or amino acid residues 221-470 of SEQ ID NO:2.

46. (original) The method of claim 38 wherein the RNase III polypeptide is exogenously added.

47. (original) The method of claim 46 wherein the RNase III polypeptide is expressed by an exogenously added vector encoding said polypeptide.

48. (original) The method of claim 38 wherein the oligomeric compound is 8 to 50 nucleobases in length and targeted to a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the compound inhibits the expression of human RNase III by at least 50%.

49. (original) The method of claim 48 wherein the oligomeric compound comprises SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 or SEQ ID NO:17.

50. (original) The method of claim 48 wherein the oligomeric compound comprises at least one chemical modification.

51. (original) The method of claim 48 wherein the oligomeric compound is targeted to a 3'-untranslated region (3'UTR), a 5'-untranslated region (5'UTR) or a coding region of a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the oligomeric compound inhibits the expression of human RNase III by at least 50%.

52. (original) The method of claim 38 wherein modulation is inhibition of expression.

53. (original) The method of claim 52 wherein RNA expression is inhibited by at least 50%.

54. (original) The method of claim 52 wherein RNA expression is inhibited by at least 70%.

55. (original) A method of modulating RNA splicing in a cell or tissue comprising contacting said cell or tissue with an amount of a modulator effective to modulate RNA splicing by at least 50% as compared to a control, wherein the modulator is a human RNase III polypeptide or an oligomeric compound targeted to a nucleic acid encoding human RNase III.

56. (original) The method of claim 55 wherein modulation of RNA splicing is determined by detecting a difference of at least 50% between a level of a splice product of the RNA in the presence of the modulator and the level of the splice product in the absence of the modulator, a difference being indicative of modulation of RNA splicing.

57. (original) The method of claim 55 wherein the RNase III polypeptide comprises an amino acid sequence which is at least 90% homologous to SEQ ID NO: 2.

58. (original) The method of claim 55 wherein the RNase III polypeptide comprises SEQ ID NO: 2.

59. (original) The method of claim 55 wherein the RNase III polypeptide comprises amino acid residues 949-1374 of SEQ ID NO:2, amino acid residues 1-220 of SEQ ID NO:2 or amino acid residues 221-470 of SEQ ID NO:2.

60. (original) The method of claim 55 wherein the oligomeric compound is 8 to 50 nucleobases in length and targeted to a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the compound inhibits the expression of human RNase III by at least 50%.

61. (original) The method of claim 60 wherein the oligomeric compound comprises SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 or SEQ ID NO:17.

62. (original) The method of claim 60 wherein the oligomeric compound comprises at least one chemical modification.

63. (original) The method of claim 60 wherein the oligomeric compound is targeted to a 3'-untranslated region (3'UTR), a 5'-untranslated region (5'UTR) or a coding region of a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the oligomeric compound hybridizes to the region of SEQ ID NO:3 and inhibits the expression of human RNase III by at least 50%.

64. (original) A method of modulating RNA translocation in a cell or tissue comprising contacting said cell or tissue with an amount of a modulator effective to modulate RNA translocation as compared to a control.

65. (original) The method of claim 64 wherein modulation of RNA translocation is determined by detecting the presence of a fragment of the RNA in a cellular compartment in the presence of the modulator and the presence of the fragment in the cellular compartment in the absence of the modulator, a difference therebetween indicative of modulation of RNA translocation.

66. (original) The method of claim 65 wherein the cell compartment is a nucleolus, nucleus or cytoplasm.

67. (original) The method of claim 64 wherein modulation of RNA translocation is determined by detecting a difference the presence of a target RNA in a cellular compartment in the presence of the modulator and the presence of the target RNA in the cellular compartment in the absence of the modulator, a difference therebetween indicative of modulation of RNA translocation.

68. (original) The method of claim 67 wherein the cell compartment is a nucleolus, nucleus or cytoplasm.

69. (original) The method of claim 64 wherein the RNase III polypeptide comprises an amino acid sequence which is at least 90% homologous to SEQ ID NO: 2.

70. (original) The method of claim 64 wherein the RNase III polypeptide comprises SEQ ID NO: 2.

71. (original) The method of claim 64 wherein the RNase III polypeptide comprises amino acid residues 949-1374 of SEQ ID NO:2, amino acid residues 1-220 of SEQ ID NO:2 or amino acid residues 221-470 of SEQ ID NO:2.

72. (original) The method of claim 64 wherein the oligomeric compound is 8 to 50 nucleobases in length and targeted to a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the compound inhibits the expression of human RNase III by at least 50%.

73. (original) The method of claim 72 wherein the oligomeric compound comprises SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 or SEQ ID NO:17.

74. (original) The method of claim 72 wherein the oligomeric compound comprises at least one chemical modification.

75. (original) The method of claim 72 wherein the oligomeric compound is targeted to a 3'-untranslated region (3'UTR), a 5'-untranslated region (5'UTR) or a coding region of a nucleic acid molecule encoding human RNase III (SEQ ID NO:3), wherein the oligomeric compound inhibits the expression of human RNase III by at least 50%.

76. (new) A method for eliciting modification of an RNA target in a cell comprising:

a) providing an RNA-like polynucleotide hybridizable with said RNA target;

b) hybridizing the RNA-like polynucleotide and the RNA to form a polynucleotide-target duplex; and

c) contacting the duplex with a polypeptide comprising an RNase III domain, under conditions selected to effect modification of the duplex by the polypeptide, and modification of the RNA target thereby.